American Journal of Hematology 60:130–135 (1999)

Pulmonary Hypertension in Patients With Myelofibrosis Secondary to Myeloproliferative Diseases

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We examined the clinical characteristics of six patients with myelofibrosis secondary to myeloproliferative diseases whose clinical courses were complicated by pulmonary hypertension to determine possible causal links between the two disorders. Six patients (four male, two female), with diagnoses of myeloproliferative disease, myelofibrosis (one with polycythemia vera, three with agnogenic myeloid metaplasia, one with unclassified myeloproliferative syndrome, one with essential thrombocytosis), and pulmonary hypertension are presented. Measurement of the pulmonary artery pressure was performed by Doppler echocardiography in all patients and by right sided heart catheterization in four patients. The range of resting pulmonary artery systolic pressure was 35 to 47 mmHg above the mean right atrium by echocardiography. One patient had autopsy evidence of pulmonary myeloid metaplasia and interstitial fibrosis; another had acute leukemic infiltration of the lung parenchyma. All patients had thrombocytosis; symptomatology in one patient with marked thrombocytosis improved with plateletpheresis. Two patients suffered systemic thrombosis. All patients had severe hepatomegaly. Two patients had evidence of left ventricular dysfunction. The interval between the development of dyspnea and death was less than seven months in five of the patients. A causal link between pulmonary hypertension and myelofibrosis secondary to myeloproliferative diseases is suggested for each patient. Hematopoietic infiltration of the pulmonary parenchyma, portal hypertension, thrombocytosis, hypercoagulability, and left ventricular failure may account in part for the development of pulmonary hypertension in these patients. Patients with myelofibrosis and dyspnea should have Doppler echocardiography to evaluate pulmonary artery pressures. Am. J. Hematol. 60:130–135, 1999. © 1999 Wiley-Liss, Inc.

Key words: myelofibrosis; myeloid metaplasia; pulmonary hypertension; myeloproliferative disorders

INTRODUCTION

Myelofibrosis, or bone marrow fibrosis, is characterized by an increase in the deposition of extracellular matrix proteins in the bone marrow stroma [1]. This histopathological entity is seen frequently in the context of the myeloproliferative diseases, and defines one form, known as agnogenic myeloid metaplasia [2]. In agnogenic myeloid metaplasia, the fibrosis of the bone marrow stroma is presumed to be a nonclonal reactive process, mediated by cytokines released from clonal hematopoietic stem cells [1,2]. In addition to myelofibrosis, agnogenic myeloid metaplasia is characterized by hepatosplenomegaly related to extramedullary hematopoiesis, and leukoerythroblastic blood changes in the peripheral smear. The annual incidence of agnogenic myeloid metaplasia is approximately 0.5/100,000 [2]. The extramedullary hematopoiesis seen in agnogenic myeloid metaplasia can involve any organ, including the thoracic structures [2–7]. Pulmonary hypertension has been reported in two cases of patients with agnogenic myeloid metaplasia [6,8].

Presented in abstract form at the 39th Annual Meeting of the American Society of Hematology, December 1997, San Diego, CA.

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Received for publication 16 July 1998; Accepted 7 October 1998

Pulmonary hypertension is defined as an elevation of the mean pulmonary artery pressure equal to or greater than 25 mmHg at rest, or 30 mmHg with exercise [9]. Pulmonary hypertension can be either primary, without any identifiable cause, or secondary to conditions such as chronic lung disease, thromboembolic disease, portal hypertension, persistent hypoxemia, and cardiac disease [9,10]. The pathophysiology of pulmonary hypertension from chronic lung disease evolves from chronic alveolar hypoxia resulting in an increase in the pulmonary artery pressure, and/or destruction of the pulmonary capillary bed, mediated first by persistent vasoconstriction and eventually by pulmonary vascular remodeling [11]. The most frequent symptoms of pulmonary hypertension are dyspnea, fatigability, chest pain, and syncope [9]. The incidence of primary pulmonary hypertension in the general population ranges from one to two cases per million [9], whereas the incidence of secondary pulmonary hypertension depends on the primary pathological condition.

In the present study, we describe six patients with myelofibrosis secondary to myeloproliferative diseases and pulmonary hypertension. The characteristics of the hematological and pulmonary syndromes are described, as well as the clinical evolution. A common link between myelofibrosis and pulmonary hypertension cannot be established for all six patients, although associations can be made for individual patients.

METHODS

Patients with myelofibrosis and echocardiographic evidence of pulmonary hypertension were identified by their respective attending hematologist. Charts were retrospectively reviewed for all outpatient visits, outpatient and inpatient studies, and summaries of hospitalizations. Information from invasive procedures, such as right heart catheterization, were obtained from the inpatient records. Diagnoses of agnogenic myeloid metaplasia, polycythemia vera, and essential thrombocytosis were established following accepted criteria [2,12,13]. In four patients, the diagnosis of pulmonary hypertension was made on the basis of a mean pulmonary artery pressure equal to or greater than 25 mmHg at rest by right heart catheterization. In two patients, the diagnosis was made noninvasively. Pulmonary artery pressures were established by echocardiographic evidence of tricuspid regurgitation flow translated to right ventricle systolic pressure and hence pulmonary artery systolic pressure above the mean right atrial pressure. To derive the estimated mean pulmonary artery pressure from the echocardiographic calculated systolic pressure, the mean right atrial pressure was assumed to be 10 mmHg. Pulmonary hypertension would therefore correspond to an echocardiographic calculated systolic pulmonary pressure of 35 mmHg above mean right atrial pressure. Doppler echocardiography was performed by the Divisions of Ultrasound and Cardiology of Thomas Jefferson University Hospital. Data from other pertinent studies are presented when available. Informed consent was obtained for all invasive procedures.

RESULTS

Six patients (four male and two female) with myeloproliferative disease had pulmonary hypertension. For a summary of patient characteristics see Tables I and II. Three of the patients presented with agnogenic myeloid metaplasia, one with polycythemia vera, one with essential thrombocytosis, and one with unclassified myeloproliferative disease. The age at presentation with myeloproliferative disease ranged from 43 to 63 years. The diagnosis of myelofibrosis was made 19 years after presentation in the patient with polycythemia vera, after six years in the patient with the unclassified myeloproliferative syndrome, and after five years in the patient with essential thrombocytosis. All patients developed dyspnea on exertion after myelofibrosis was detected, (range 0 months to 93 months after diagnosis). Pulmonary hypertension was detected after the development of dyspnea in less than three months in five patients and 124 months in the sixth. All patients except patient 2 received hydroxyurea prior to developing dyspnea. Five patients died between one month to seven months after developing dyspnea. All patients had undergone splenectomy. Biopsies of splenic tissue showed extramedullary myeloid metaplasia in all cases. Dyspnea anteceded splenectomy in three cases (range 9 months prior to splenectomy to 3 years after splenectomy). The interval between splenectomy and death ranged from 1 month to 43 months.

All patients had pulmonary pressure estimates by Doppler echocardiography with a range of pulmonary artery systolic pressure of 35 to 47 mmHg above the mean right atrial pressure. Right heart catheterization confirmed pulmonary hypertension in four patients. All patients except one (patient 5) had ventilation perfusion scans performed, all were low probability for pulmonary embolism except one intermediate (patient 1). Two patients (patients 1 and 5) had documented evidence of venous and arterial thrombosis. All patients had marked hepatosplenomegaly. Only patient 6 was an active smoker at the time of the diagnosis. Vascular congestion was detected by chest radiography in patients 1, 3, and 5. Pulmonary function testing was performed in four patients. It showed a restrictive pattern in patients 3, 4, and 6 and decreased diffusion capacity and mild hypoxia in patient 2. Tc-99m sulfur colloid imaging for extramedullary hematopoiesis was performed in two patients, numbers 1 and 4, and failed to show pulmonary uptake in either of them. Autopsies were performed in two patients

TABLE I. Patient Characteristics*

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Gender	Male	Female	Male	Male	Male	Female
Age, years	73	43	51	49	65	68
DX	PV	AMM	AMM	AMM	MPS	ET
PAP						
ECHO	38 mmHg	35 mmHg	47 mmHg	35 mmHg	43 mmHg	41 mmHg
RSHC	56/25	Not done	80/35	55/22	Not done	57/26
Mean	36 mmHg		50 mmHg	36 mmHg		36 mmHg
PAWP	18 mmHg		18 mmHg	13 mmHg		12 mmHg

*Age: Age at the time of diagnosis of myelofibrosis. DX, initial myeloproliferative diagnosis; PV, polycythemia vera; AMM, agnogenic myeloid metaplasia; MPS, myeloproliferative syndrome; ET, essential thrombocytosis; ECHO, Doppler echocardiography measurements of the pulmonary artery systolic pressure above the mean right atrial pressure; RSHC, measurement of the systolic and diastolic pulmonary artery pressures by right side heart catheterization; Mean, mean pulmonary artery pressure calculated by RSHC; PAWP, pulmonary artery wedge pressure.

TABLE II. Clinical Evolution: Intervals Between Different Events in Months*

Patient	MF DX to DOE	DOE to PHT DX	DOE to death	Splenectomy to death
1	0	1	6	3
2	62	124	Alive	Alive
3	93	3	7	3
4	77	0	6	35
5	46	1	3	43
6	20	0	1	1

*DX, diagnosis; MF, myelofibrosis; DOE, dyspnea on exertion; PHT, pulmonary hypertension.

(see below: patients 3 and 6). The following is a descriptive summary of each patient.

Patient 1

Patient 1, a white male, was 54 years of age in 1974 when polycythemia vera and an inferior wall myocardial infarction were diagnosed. The patient developed progressive splenomegaly and thrombocytosis and had a transient cerebral ischemic attack in 1988. In November 1993 he developed progressive anemia, mild renal failure, weakness, dyspnea on exertion and myelofibrosis was diagnosed. An echocardiogram in December 1993 showed a mildly dilated left ventricle, inferoposterior akinesis, dilated left and right atria, and a systolic pulmonary artery pressure 38 mmHg greater than the mean right atrial pressure. In February 1994 splenectomy was performed and was complicated by femoral and portal vein thrombosis, and anasarca. Right side heart catheterization was performed in March 1994. The pulmonary artery pressure was 56/25 mmHg with a mean of 36 mmHg and a pulmonary capillary wedge pressure of 18 mmHg. This study also showed nonobstructive coronary artery disease and global hypokinesis with a left ventricular ejection fraction of 29%. The patient died at home in May 1994.

Patient 2

Patient 2, a 43-year-old white female, was diagnosed with agnogenic myeloid metaplasia and beta thalassemia trait in 1981. In 1986 she developed dyspnea on exertion. In 1992 she developed progressive splenomegaly and anemia. In August 1993 she underwent splenectomy, complicated by marked thrombocytosis, with platelet counts as high as 1.5×10^6 platelets/μL, and worsening dyspnea. In April and October of 1995, the patient had normal echocardiograms, but a repeat study in December 1996 showed a dilated left atrium with no other chamber or valvular abnormalities, and an estimated systolic pulmonary artery pressure of 35 mmHg above the mean right atrial pressure. Dyspnea has been markedly alleviated by plateletpheresis on several occasions. The patient is alive.

Patient 3

Patient 3, a white male, was 51 years of age in 1984 when a diagnosis of agnogenic myeloid metaplasia was made. The patient developed progressive hepatosplenomegaly, and in February 1992 he developed mild dyspnea on exertion, anemia, and progressive cachexia. Echocardiogram in May 1992 demonstrated mildly dilated right ventricle, right and left atrium, and a septal

contraction abnormality secondary to elevated right ventricular pressure. The systolic pulmonary artery pressure was 47 mmHg greater than the mean right atrial pressure. The patient underwent splenectomy in June 1992. Preoperative right side heart catheterization showed a pulmonary artery pressure of 80/35 mmHg, with a mean pressure of 50 mmHg, and a pulmonary wedge pressure of 18 mmHg. The patient died without leaving the hospital in September 1992 after a complicated clinical course, characterized by inadequate ventilation and pulmonary consolidation. On autopsy, the pulmonary interstitial spaces were filled with mature and immature hematopoietic cells representing pulmonary myeloid metaplasia.

Patient 4

Patient 4 was a 49-year-old white male diagnosed in 1986 with agnogenic myeloid metaplasia. In January 1990 the patient underwent splenectomy complicated by severe thrombocytosis. In June 1992 the patient developed dyspnea on exertion, peripheral edema, and progressive hepatomegaly. Echocardiogram showed a systolic pulmonary artery pressure 35 mmHg above the mean right atrial pressure (48 mmHg in September 1992) normal right and left ventricles, dilated right and left atria. In July 1992 the patient developed chronic nonproductive cough and severe jugular venous distention. Left ventricular ejection fraction was 65%. Right side heart catheterization in October 1992 showed a pulmonary artery pressure of 55/22 mmHg with a mean of 36 mmHg and a pulmonary wedge pressure of 13 mmHg. The clinical condition continued to deteriorate with progressive respiratory symptoms. The patient died in December 1992 after an episode of pulmonary hemorrhage.

Patient 5

Patient 5, a white male, was 59 years of age in August 1987 when he was diagnosed with an unclassified myeloproliferative syndrome characterized by leukocytosis and thrombocytosis. In August 1993 he developed features of myelofibrosis, confirmed by bone marrow biopsy, and a hypercoagulable state including acute coronary thrombosis in January 1994 and cerebrovascular accident in 1996. In March 1994 the patient underwent splenectomy, which revealed myeloid metaplasia. In June 1997 the patient developed dyspnea. An echocardiogram in July 1997 showed mild concentric left ventricular hypertrophy, inferoposterior hypokinesis, dilated left and right atrium, and a systolic pulmonary artery pressure 43 mmHg above the mean right atrial pressure. The patient died in October 1997 from head trauma.

Patient 6

Patient 6 was a 63-year-old African American female diagnosed with essential thrombocytosis in 1990. In 1994 she developed progressive splenomegaly. In February 1995 myelofibrosis was diagnosed. Around October 1996 the patient developed dyspnea on exertion. Echocardiogram showed a markedly dilated right ventricle, right ventricular hypokinesis, and dilated left and right atria with an estimated systolic pulmonary artery pressure 41 mmHg above the mean right atrial pressure. The patient underwent splenectomy in October 1996. Measurements of the pulmonary artery pressure postoperatively by right side heart catheterization were 57/26 mmHg, with a mean of 36 mmHg, and a pulmonary wedge pressure of 12 mmHg. The patient died in November 1996 from progressive respiratory failure. On autopsy, lung sections showed evidence of acute leukemic infiltration, involving the interstitial and perivascular spaces, consistent with acute leukemic transformation of agnogenic myeloid metaplasia.

DISCUSSION

We have described six patients with myeloproliferative diseases with myelofibrosis and pulmonary hypertension. All patients were evaluated by Doppler echocardiography. This noninvasive technique is an accepted means of determining the pulmonary artery pressure [14]. In four of these patients, the pulmonary artery pressure was directly measured via right side heart catheterization, confirming the diagnosis of pulmonary hypertension.

There are several possible pathophysiological links in our patients between the developments of myelofibrosis and pulmonary hypertension. Patient 3 had evidence of pulmonary myeloid metaplasia and fibrosis on postmortem examination. Patient 6 had postmortem evidence of perivascular interstitial acute leukemic infiltration. None of the other patients had infiltrates by chest X-ray; and in patients 1 and 4, Tc-99m sulfur colloid scanning, a technique used to detect hematopoietic tissue [6], did not show evidence of pulmonary uptake, excluding pulmonary myeloid metaplasia in these patients. In cases numbers 3 and 6, pulmonary parenchymal infiltration by hematopoietic cells may explain the pulmonary symptoms. Although myeloid metaplasia occurs mainly in the liver, spleen, and lymph nodes [3], virtually any organ can be infiltrated with hematopoietic tissue in patients with myelofibrosis [2–4]. A patient with a myeloproliferative syndrome complicated by pulmonary myeloid metaplasia, pulmonary fibrosis, pulmonary hypertension, and a fatal outcome, has been reported [6]. Both platelet derived growth factors and transforming growth factors have been implicated in the stimulation of fibroblasts in myelofibrosis [1]. An experimental animal model has been described in which transgenic mice overexpressing thrombopoietin, a megakaryocytic stimulatory factor, developed myelofibrosis mediated by platelet derived

growth factors and transforming growth factor [15]. Platelet derived growth factor expression increases in animal lungs with hypoxic pulmonary hypertension [11,16]. Although the role of platelet derived growth factor in the structural remodeling in pulmonary hypertension is not known, it is intriguing that in patient 3 and in the patients described in references 6 and 7, there was evidence of concomitant pulmonary fibrosis.

All patients had moderate to severe thrombocytosis. In case number 2, severe thrombocytosis relates to dyspnea, since it improves when the platelet count is reduced by plateletpheresis. One case of pulmonary hypertension has been described in a patient with myeloid metaplasia postsplenectomy complicated by severe thrombocytosis. The patient's signs and symptoms improved once the platelet count was corrected [8]. One patient with thrombocytosis and pulmonary hypertension has been reported with evidence of pulmonary platelet activation and thrombin generation [17]; the patient's symptoms improved with the combined use of heparin and acetylsalicylic acid. Patients 3, 4, and 6 had mild elevation of d-dimers, suggesting chronic low grade intravascular coagulation. Patients 1 and 5 suffered hypercoagulable states, as manifested by arteriovenous thrombosis. Although only patient 1 had an intermediate probability ventilation perfusion scan for pulmonary embolism, this does not exclude the possibility that pulmonary microthrombosis related to thrombocytosis could have a role in the development of pulmonary hypertension in these patients. It is known that the metabolism of prothrombin and fibrinogen is increased in patients with myeloproliferative diseases and thrombocytosis, and that these parameters normalize after therapeutic reduction of the platelet count [18], suggesting that chronic intravascular coagulation is not uncommon in these patients, as is reflected by the elevated d-dimers in patients 3, 4, and 6. Studies using prostacyclin, an inhibitor of platelet aggregation and vasodilator, in primary pulmonary hypertension have suggested a role of platelet function in pulmonary hypertension [19].

In all cases, complaints of dyspnea occurred in parallel with the development of progressive hepatomegaly. The actuarial risk of death from portal hypertension in patients with agnogenic myeloid metaplasia is 7% at 5 years [20], and 17% of the patients in a series of patients with myelofibrosis had esophageal varices [21]. The relationship between portal hypertension and pulmonary hypertension is well known [22]. Of twelve cases presented in this report, eight of the 12 patients had histologic evidence of thromboembolism in conjunction with pulmonary vascular plexiform changes [22]. In view of the severity of the hepatosplenomegaly in our patients with myeloproliferative disease, portal hypertension could have played a role in the development of pulmonary hypertension.

There is no relationship between splenectomy and the development of pulmonary hypertension in our patients. The clinical postsplenectomy course in patients with myelofibrosis has been well described [23] and, although cardiopulmonary complications are not clearly described, two patients died from congestive heart failure and three from unspecified thromboembolic events in that study.

Two patients had elevated pulmonary capillary wedge pressures (patients 1 and 3), indicating some degree of left ventricular failure. Although neither had evidence of significant valvular disease, the left ventricular dysfunction could have contributed to the development of the pulmonary hypertension. Patient 1 had a history of inferior wall myocardial infarction, and coronary angiogram showed diffuse left ventricular hypokinesis but no evidence of critical coronary artery disease. In both cases mild volume overload could have contributed to the elevation of the pulmonary wedge pressure.

In an echocardiographic evaluation of 30 patients with myeloproliferative disorders, pulmonary hypertension was detected in four patients with polycythemia vera, but none of the four patients with agnogenic myeloid metaplasia evaluated in that study had evidence of pulmonary hypertension [24]. However, the hematological and clinical status of the patients were not described. Death from cardiovascular complications, including congestive heart failure, is frequent in patients with myelofibrosis (12.2% in reference 20 and 41.8 % in reference 21).

The clinical evolution of our patients was faster than reported for patients with primary pulmonary hypertension [9]. Five patients died less than seven months after the initiation of symptoms, although three of them (patients 1, 3, and 6) already had a very poor performance status at the time of initiation of symptoms. Patient 5 died from trauma three months after symptomatology appeared. One patient is alive and well almost five years after initial symptoms.

Only palliative therapy exists for most patients with myelofibrosis, except for bone marrow transplantation in a selected group of patients with myelofibrosis [25]. Anticoagulation with warfarin is recommended as therapy in primary pulmonary hypertension [9], and has been shown to be of benefit in a patient with thrombocytosis and pulmonary hypertension, when combined with antiplatelet therapy [17]. The fact that thrombocytosis and thrombosis may have contributed to the development of pulmonary hypertension in some of our patients suggests that anticoagulation and antiplatelet therapy should be considered as well for patients with both pulmonary hypertension and myelofibrosis. However, the management should be individualized since some of these patients have a bleeding diathesis [2], portal hypertension, and esophageal varices.

In conclusion, we have described the clinical course and characteristics of six patients with myelofibrosis and pulmonary hypertension. Hematopoietic infiltration of the lung parenchyma, thrombocytosis, thromboembolism, portal hypertension, and left ventricular failure may have roles in the development of the syndrome. All patients with myelofibrosis and dyspnea should have Doppler echocardiography to evaluate cardiac valvular disease and pulmonary artery pressure.

REFERENCES

1. Reilly JT. Pathogenesis of idiopathic myelofibrosis: present status and future directions. Br J Haematol 1994;88:1.
2. Tefferi A, Silverstein MN, Noel P. Agnogenic myeloid metaplasia. Semin Oncol 1995;22:327.
3. Pitcock JA, Reinhard EH, Justus BW, Mendelsohn RS. A clinical and pathological study of seventy cases of myelofibrosis. Ann Intern Med 1962;57:73.
4. Glew RH, Haese WH, McIntyre P. Myeloid metaplasia with myelofibrosis. The clinical spectrum of extramedullary hematopoiesis and tumor formation. Johns Hopkins Med J 1973;132:253.
5. Yusen RD, Kollef MH. Acute respiratory failure due to extramedullary hematopoiesis. Chest 1995;108:1170.
6. Coates GG, Eisenberg B, Dail DH. Tc-99m sulfur colloid demonstration of diffuse pulmonary interstitial extramedullary hematopoiesis in a patient with myelofibrosis. Clin Nucl Med 1994;19:1079.
7. Asakura S, Colby TV. Agnogenic myeloid metaplasia with extramedullary hematopoiesis and fibrosis in the lung. Chest 1994;105:1866.
8. Marvin KS, Spellberg RD. Pulmonary hypertension secondary to thrombocytosis in a patient with myeloid metaplasia. Chest 1993;103: 642.
9. Rubin LJ. Primary pulmonary hypertension. N Engl J Med 1997;336: 111.
10. Fedullo PF, Moser KM. Advances in acute pulmonary embolism and chronic pulmonary hypertension. Adv Intern Med 1997;42:67.
11. Vender RL. Chronic hypoxic pulmonary hypertension. Chest 1994; 106:236.
12. Berk PD, Goldberg JD, Donovan PB, Fruchtman SM, Berlin NI, Wasserman LR. Therapeutic recommendations in polycythemia vera based on Polycythemia Vera Study Group protocols. Semin Hematol 1986;23:132.
13. Tefferi A, Silverstein MN, Hoagland HC. Primary thrombocythemia. Semin Oncol 1995;22:334.
14. Martin-Duran R, Larman M, Trugeda A, Vazquez De Prada JA, Ruano J, Torres A, Figueroa A, Pajaron A, Nistal F. Comparison of Doppler-determined elevated pulmonary arterial pressure with pressure measured at cardiac catheterization. Am J Cardiol 1986;57:859.
15. Yan X-Q, Lacey D, Hill D, Chen Y, Fletcher F, Hawley RG, McNiece IK. A model of myelofibrosis and osteosclerosis in mice induced by overexpressing thrombopoietin (mpl ligand): reversal of disease by bone marrow transplantation. Blood 1996;88:402.
16. Katayose D, Ohe M, Yamauchi K, Ogata M, Shirato K, Fujita H, Shibahara S, Takishima T. Increased expression of PDGF A- and B-chain genes in rat lungs with hypoxic pulmonary hypertension. Am J Physiol 1993;264:L100.
17. Rostagno C, Prisco D, Abbate R, Poggesi L. Pulmonary hypertension associated with longstanding thrombocytosis. Chest 1991;99:1303.
18. Martinez J, Shapiro SS, Holburn R. Metabolism of prothrombin and fibrinogen in patients with thrombocytosis secondary to myeloproliferative states. Blood 1973;42:35.
19. McLaughlin VV, Genthner DE, Panella MM, Rich S. Reduction in pulmonary vascular resistance with long-term epoprostenol (prostacyclin) therapy in primary pulmonary hypertension. N Engl J Med 1998; 338:273.
20. Dupriez B, Morel P, Demory JL, Lai JL, Simon M, Plantier I, Bauters F. Prognostic factors in agnogenic myeloid metaplasia: a report of 195 cases with a new scoring system. Blood 1996;88:1013.
21. Ward HP, Block MH. The natural history of agnogenic myeloid metaplasia (AMM) and a critical evaluation of its relationship with the myeloproliferative syndrome. Medicine 1971;50:357.
22. Edwards BS, Weir K, Edwards WD, Ludwig J, Dykoski RK, Edwards JE. Coexistent pulmonary and portal hypertension: morphologic and clinical features. J Am Coll Cardiol 1987;10:1233.
23. Brenner B, Nagler A, Tatarsky I, Hashmonai M. Splenectomy in agnogenic myeloid metaplasia and postpolycythemic myeloid metaplasia. Arch Int Med 1988;148:2501.
24. Reisner SA, Rinkevich D, Markiewicz W, Tatarsky I, Brenner B. Cardiac involvement in patients with myeloproliferative disorders. Am J Med 1992;93:498.
25. Anderson JE, Sale G, Appelbaum FR, Chauncey TR, Storb R. Allogeneic marrow transplantation for primary myelofibrosis and myelofibrosis secondary to polycythaemia vera or essential thrombocytosis. Br J Haematol 1997;98:1010.